

Remarks

Reconsideration of this Application is respectfully requested.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

The Examiner has rejected claims 1-7 and 18-20 under 35 U.S.C. § 103(a) as being unpatentable over Stier *et al.* in view of Kirk *et al.* and Easton *et al.* Applicants respectfully traverse this rejection.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. In particular, the M.P.E.P. sets forth the criteria necessary to satisfy this burden:

To establish a *prima facie* case of obviousness, three basic criteria *must* be met. First, there *must* be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there *must* be a reasonable expectation of success. Finally, the prior art reference (or references when combined) *must* teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success *must* both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

See M.P.E.P., Eighth ed., February revision, § 2142 "Legal Concept of *Prima Facie* Obviousness," (2003, emphasis added). Applicants respectfully assert that the references cited in support of the 35 U.S.C. § 103 rejection do not meet these criteria, and that consequently the Examiner has not established a *prima facie* case of obviousness.

In regard to the first criterion, a *prima facie* case of obviousness has not been made because there is no suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art at the time of invention, to modify Stier *et al.* or to combine Stier *et al.* with Kirk *et al.* or Easton *et al.* to arrive at the claimed methodology. Stier *et al.* teach that an angiotensin II receptor antagonist, Losartan, may *prevent* stroke. This is apparent from the Materials and Methods and the Results sections of Stier *et al.* See pp. S38-9. Stroke-prone spontaneously hypertensive rats are administered drug chronically, beginning at 8.4 weeks of age. The aim is to reduce hypertension through systemic effects of the drug, i.e., to reduce circulating angiotensin, thereby reducing plasma Na⁺ and enhancing kidney function. Stier *et al.* suggest that angiotensin II contributes to the *development* of strokes in the rat model. *Id.* at S41, right column, lines 7-8. Kirk *et al.* disclose that angiotensin II receptor antagonists are useful for lowering hypertension. Easton *et al.* discuss hypertension as a risk factor for the development of atherosclerosis which is a major cause of strokes. See p. 2337, left column, under "Atherosclerosis Risk Factors." Easton *et al.* also outline standard therapies for ischemic events on page 2339 under "Acute Management." "When cerebral infarction occurs, the immediate goal is to optimize cerebral perfusion of the ischemic area." *Id.* Thus, there is no suggestion or motivation to combine the teachings of the above-cited references to arrive at a method for preventing damage to the excitable cells that express a transient K⁺ current in a patient who has undergone or is undergoing an ischemic event by administering an angiotensin II receptor antagonist which increases a transient K⁺ current in said cells.

The Examiner asserts that a skilled artisan would have been motivated to treat a patient suffering from a stroke by *initiating* treatment with an anti-hypertensive medication. See Paper No. 19, p. 4, lines 3-6. The reasoning is that because hypertension can lead to atherosclerosis which, in turn, can cause an ischemic event, one would treat hypertension to control the effects of the stroke. However, in fact such treatment is contraindicated in the cited art: "Elevated blood pressure should not be lowered unless there is malignant hypertension []." See Easton *et al.*, p. 2339, left column, under "Acute Management." Further, there are other risk factors for the development of atherosclerosis such as old age, diabetes mellitus, elevated blood cholesterol and tobacco smoking. *Id.* at p. 2337, left column, lines 8-12. Thus, there is no support for a general conclusion that at the time of invention a skilled artisan would have presumed that hypertension caused atherosclerosis, which, in turn, resulted in a stroke. Because it is known that there are many factors that can lead to atherosclerosis, a skilled artisan would not presume to try to lower blood pressure, for example, over lowering blood cholesterol during the ischemic event. Moreover, a physician following a standard protocol would not even treat any underlying cause during the ischemic event, rather she would prescribe drugs such as blood clot dissolvers, glutamate antagonists, Ca^+ channel antagonists and calcium-activated K^+ channel antagonists. See Specification, p. 3, ¶0006. At the time of invention there was no suggestion or motivation in the art that an angiotensin II receptor antagonist is indicated for the treatment of a stroke. Because such treatment is neither the prevailing protocol or suggested in the art, it would not have been *prima facie* obvious for a skilled artisan to prevent damage to the excitable cells of a patient that express a transient K^+ current

during or after said patient undergoes or has undergone an ischemic event by administering an effective amount of an angiotensin II receptor antagonist.

A *prima facie* case of obviousness has not been made because neither the references alone or in combination teach or suggest all the claim limitations as required by the second criterion. The Examiner acknowledges that, "Stier *et al.* do not expressly disclose administration of Losartan during or after a stroke." See Paper No. 17, p. 3. As stated above, Kirk *et al.* disclose that an angiotensin II receptor antagonist is useful for lowering hypertension. As stated above, Easton *et al.* disclose that hypertension may cause atherosclerosis, which is a leading cause of stroke. However, none of the cited references alone or taken together teach administering an angiotensin II receptor antagonist during or after a stroke.

Further, there would have been no reasonable expectation of success as required by the third criterion to administer an angiotensin II receptor antagonist during or after an ischemic event as presently claimed. There is no teaching or suggestion in the art that administering an angiotensin II receptor antagonist to increase the K^+ current in excitable cells is useful during or after a stroke to prevent damage to said excitable cells. The above-cited references only reflect the prevailing paradigm of reducing a risk factor, hypertension, so as to prevent a stroke. According to this paradigm, long term treatment with anti-hypertensives is the norm for *preventing* a stroke. Absent the teachings in Applicants' specification, the skilled artisan would not regard the preventive methodology of Stier *et al.* as useful in the acute management of strokes discussed by Easton *et al.* Applicants respectfully assert that the Examiner has improperly relied upon hindsight reasoning.

The Examiner asserts that it would have been *prima facie* obvious for a person of ordinary skill in the art to continue the treatment of a hypertensive patient undergoing an ischemic event with an anti-hypertensive medication, and that such administration would inherently increase a transient K^+ current in the excitable cells of a patient. Paper No. 19, p. 4, line 8 - p. 6 line 9. "In relying upon the theory of inherence, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art." See M.P.E.P. § 2112. The data in Stier *et al.* show that there is a dissociation between anti-hypertensive effects and the vascular protective effects of Losartan in the stroke model. See also Specification, p. 4, lines 4-8 (citing additional references). Stier *et al.* state that "[d]espite a continued rise in systolic blood pressure to severely hypertensive levels at either dose in the losartan-treated SHRSP, no strokes were recorded during this experiment." *Id.* at S39. "[T]he vascular protective effects of these agents can be dissociated, at least in part, from their anti-hypertensive action." *Id.* at S41. For at least the reason that Stier *et al.* establishes that Losartan's anti-hypertensive effect and its vascular protective properties are distinct and are not concomitant, the Examiner has not shown that the allegedly inherent characteristic of increasing a transient K^+ current in excitable cells by treating hypertension with an angiotensin II receptor antagonist necessarily flows from the applied prior art. In fact, the applied prior art teaches that the anti-hypertensive action of Losartan is independent of certain other actions. Thus, the Examiner has not provided evidence as required under M.P.E.P. § 2112, to show that treatment of hypertension with an angiotensin II receptor antagonist inherently increases the transient K^+ current in excitable cells. Applicants respectfully

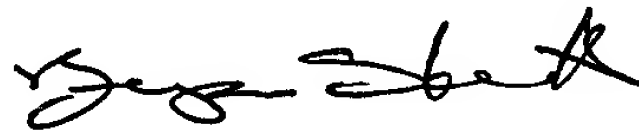
remind the Examiner that inherency may not be established by a possibility that the characteristic exists. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient." See M.P.E.P. § 2112 (quoting from *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). Therefore, the Examiner has not provided the requisite support required to establish her *prima facie* obviousness rejection under 35 U.S.C. § 103. Applicants respectfully request that this rejection be withdrawn.

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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